SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
RESEARCH UNIT OF MEMORIAL CENTER
FOR CANCER AND ALLIED DISEASES
410 EAST 68TH STREET
NEW YORK 21, NEW YORK

September 8, 1954

Dr. Joshua Lederberg
Professor of Genetics
The University of Wisconsin
Madison 6, Wisconsin

Dear Dr. Lederberg:

Your letter of August 29 to Dr. Rhoads has been brought to my attention, and we have sent to you, yesterday, 100 mg. of azaserine. This has been supplied to us by the Parke Davis Company, and I am confident that, should you desire more, they would be glad to furnish it. I would suggest that you write to Dr. Leon Sweet for any additional material. I am certain that you will find this material of interest. Dr. Demerec has already reported to us that it is one of the most mutagenic agents he has studied.

Sincerely yours,

C. Chester Stock

C. Chester Stock, Ph.D., Chief
Division of Experimental Chemotherapy

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cc: Dr. C. P. Rhoads

APR 14 1981

Sawhill T
Bristol Myers Award for Cancer Research

# DIRECTIONS FOR ADMINISTERING COLEY'S TOXINS

It is essential to follow the directions very carefully:

1. Keep the bottle of toxins in a refrigerator, $2^{o}$ - $8^{o}$ C. ($35^{o}$ - $46^{o}$ F.)
2. For intravenous therapy use tuberculin syringe and 25-gauge needle.
3. For intratumoral or intramuscular injections use a Becton-Dickinson tuberculin syringe with a 21 or 22-gauge two-inch needle.
4. Under strick asepsis withdraw the toxins from the rubber-capped vial. For dilution use sterile isotonic saline solution, triple distilled water or sterile water, in the smaller doses only (up to 0.5 cc.). Care should be taken in making the dilutions. For example if one wishes to give 1/80 of a minim, take one minim of toxin and draw up additional saline to the 10 minim mark; then expel all but one minim (that leaves 1/10 of a minim in the syringe at this point.) Then draw up again with additional saline to the 8 minim mark and expel all but one minim which then leaves 1/80 of a minim of toxin in the syringe. One can then draw up 8 or 10 minims additional saline which still leaves 1/80 of a minim in the syringe but gives additional bulk. A similar method of calculating should be carried out for the other doses that have been suggested. Avoid escape of any of the solution outside of the vein.

## SUGGESTED DOSAGE*

### Intravenous Therapy

| | | |
|---|---|---|
| 1st dose | 1/80 minim | 0.001 cc. |
| 2nd | 1/60 | 0.002 |
| 3rd | 1/30 | 0.003 |
| 4th | 1/15 | 0.006 |
| 5th | 1/5 | 0.012 |
| 6th | 1/2 | 0.030 |
| 7th | 1 | 0.06 |
| 8th | 2 | 0.12 |
| 9th | 4 | 0.25 |
| 10th | 6 | 0.36 |
| 11th | 8 | 0.50 |
| 12th | 10 | 0.60 |
| 13th | 12 | 0.75 |
| 14th | 16 | 1.00 |

### Intratumoral Therapy

| | | |
|---|---|---|
| 1st dose | 1/2 minim | 0.03 cc. |
| 2nd | 1 | 0.06 |
| 3rd | 1 1/2 | 0.09 |
| 4th | 2 | 0.12 |
| 5th | 4 | 0.25 |
| 6th | 6 1/2 | 0.40 |
| 7th | 9 | 0.55 |
| 8th | 12 | 0.75 |
| 9th | 14 | 0.85 |
| 10th | 16 | 1.00 |

### Intramuscular Therapy

| | | |
|---|---|---|
| 1st dose | 1 minim | 0.06 cc. |
| 2nd | 3 | 0.18 |
| 3rd | 5 | 0.30 |
| 4th | 8 | 0.50 |
| 5th | 10 | 0.60 |
| 6th | 12 | 0.75 |
| 7th | 14 | 0.85 |
| 8th | 16 | 1.0 |
| 9th | 18 | 1.1 |
| 10th | 20 | 1.2 |

NOTE: Each case must be treated individually, the reaction being ascertained by careful observation. The need for increasing the dose is governed by the febrile reaction and chills, and it should be increased less rapidly on elderly or cachectic patients. The aim is to produce a marked constitutional effect, with a chill and temperatures of $103^{o}$ to $105^{o}$ F. Chills usually occur 15 to 60 minutes after an intratumoral or intravenous injection. Temperatures should be recorded at 15 or 30 minute intervals until it is evident that the peak elevation has passed and temperature is falling (usually 2 hours after injection). Also duration of actual chill should be recorded. Daily injections are the rule. The temperature will rise rapidly after a chill and the entire reaction will be over within a few hours following intratumoral or intravenous injections; intramuscular injections produce slower and much more prolonged reactions. There may also be profuse sweating, headache and muscular aching. Pain during the reaction may be localized in the area of the tumor. In treating children, the dose should be reduced proportionately at first, according to the body weight. It may then be increased rapidly. Great caution is recommended in treating elderly patients. Intravenous therapy is recommended because of lack of local reaction and pain; injections by this route produce rapid diffusion of the toxins.

* In giving the dosage in both minims and cc. the equivalents are not exactly even; they have been given as nearly as possible so as to make easily measurable doses.

## DIRECTIONS FOR ADMINISTERING COLEY'S TOXINS

SITE: It appears to be necessary for the toxins to reach the neoplastic cells as rapidly as possible after injections in order to produce the best results. Rapidity of absorption is therefore an important factor.

Intravenous: It appears that this site is most effective and is usually preferred by the patients, as the entire reaction is of shorter duration. Increase the dosage cautiously once the point has been reached where marked reactions with chills and fever to 105° F. are obtained. A little practice with the syringe will suggest ways in which one can make the dilution readily and accurately. An error in calculating intravenous dosage might be extremely hazardous, especially if the patient is over 60, when too severe a reaction might act as an exciting cause of a cerebro-vascular accident: in such cases it is suggested that the same dose be given intravenously until it fails to produce a reaction of 102° to 105° F., then proceed to the next larger dose.

Intratumoral: These should be given deeply into the tumor or its immediate periphery, using a fine gauge needle of sufficient length. If the needle penetrates a necrotic portion of the tumor no reaction may occur, while if a vein is pricked with the slightly higher dosage suggested for intratumoral use, a profound reaction may result. Do not attempt intratumoral injections in bone tumor cases, although injections in the immediate periphery may prove effective. For carcinoma, make the initial injection into the tumor or within an inch of its periphery, alternating every 24 hours with an intravenous injection. If the tumor is inaccessible, use intravenous alone, or combined with intramuscular therapy, using the dosages suggested for each route.

Intramuscular: These may be given deeply into the gluteal or deltoid muscles, massaging the site with an alcohol sponge for a few minutes after withdrawing the needle. The usual precautions against making an injection inadvertently into a deep vein should be observed. Do not use subcutaneous injections; they are ineffective and may cause painful indurations due to slow, incomplete absorption. Do not inject the same site again; keep at least an inch away from previous sites, or a Shwartzman reaction may be elicited.

FREQUENCY: Injections should be given daily at first, or every other day, depending on the condition of the patient. Try to give a maximum of 6 injections a week or, if this is not possible, 4 a week for the first three weeks of treatment. After a particularly profound reaction it is best to wait 48 hours before resuming injections. A continued fever in certain advanced cases, where rapid destruction of neoplastic tissue causes toxemia from absorption, may be an indication for stopping the treatment for a few days. After 15 or 20 injections, a rest period of three weeks may be given. During this interval, if there is any evidence of increased activity in the tumor, injections should be resumed at once. When resuming treatment after a rest period, always begin with the minimum dose, as susceptibility is usually regained. When tolerance is again ascertained, the dose may be increased accordingly.

DURATION: Until further research has determined the minimum safe duration for each type of tumor, it is advisable to continue the injections (with intervals of three weeks' rest) for some time after the tumor has regressed - that is, for about six months. After surgical removal of a tumor, injections should be begun as soon after operation as possible, (3 or 4 days) and given both intravenously and intramuscularly.

## DIRECTIONS FOR ADMINISTERING COLEY'S TOXINS

### GENERAL CONSIDERATIONS:

(a) It is not usually necessary to keep the patient in bed, except during the chill and maximum febrile reaction. However, plenty of rest and a nourishing diet are essential. If the patient is markedly anemic, transfusions appear to be of value.

(b) It is important to plan the time of the injections so that they do not interfere with maintenance of an adequate diet. Never give one before or after a meal (the stomach should be empty; patients have little appetite for several hours after an injection). A suitable time is 1 1/2 hours after breakfast or the mid-day meal. If injections are given in the morning, the patient will not want lunch, but by evening usually feels like a substantial meal. If the injection is given in the afternoon, give the main meal at noon, and a light supper at night. Give fluids as needed so that the patient does not become dehydrated.

(c) The temperature and pulse should be recorded every 15 or 30 minutes after each injection until the febrile reaction has subsided, a matter of about four or five hours. There is marked variation in the individual response; the same dose may evoke a marked reaction in one patient, little or none in another. Therefore it is difficult to formulate directions which will apply to all cases. The age and general condition of the patient, the tissue permeability and other factors governing rapidity of absorption, the site and duration of the disease must all be taken into consideration. The physician must increase the dose according to the individual response to the preceding dose, bearing in mind that the aim is to secure successive febrile reactions and chills. If too large a dose is given patients may develop dyspnea or become slightly disoriented for one or two hours.